Redetermination of the structure of olmesartan medoxomil, (5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl)-methyl-4-(2-hydroxypropan-2-yl)-2-propyl-1-(-[2-(2*H*-1,2,3,4-tetrazol-5-yl)-phenyl]phenylmethyl)-1*H*-imidazole-5-carboxylate, $C_{29}H_{30}N_6O_6$

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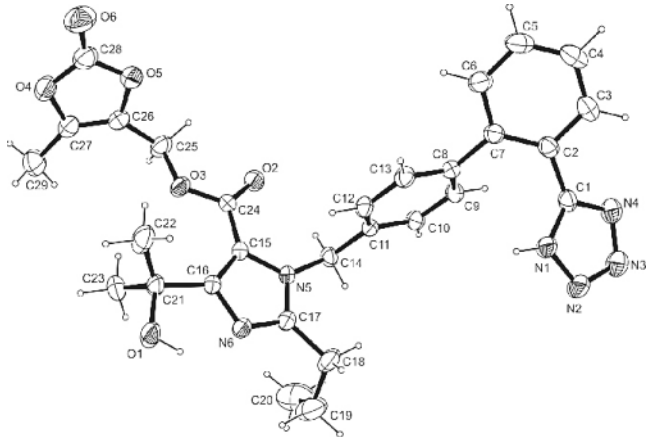

Abstract

$C_{29}H_{30}N_6O_6$, monoclinic, $P2_1/c$ (no. 14), a = 12.3134(3) Å, b = 21.2095(4) Å, c = 10.8503(2) Å, β = 100.549(1)°, V = 2785.8 Å^3, Z = 4, $R_{gt}(F)$ = 0.0422, $wR_{ref}(F^2)$ = 0.1205, T = 200 K.

Table 1. Data collection and handling.

Crystal:	colourless blocks, size 0.28×0.41×0.46 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.95 cm^{-1}
Diffractometer, scan mode:	Bruker APEX-II CCD, φ and ω
$2\theta_{max}$:	56.64°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	27416, 6938
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 5909
$N(param)_{refined}$:	379
Programs:	SHELX [6], ORTEP-3 [7], MERCURY [8], PLATON [9]

Source of material

The title compound was obtained as a gift sample from Jubilant Life Sciences Ltd., Noida, India. The compound was recrystallized from methanol by slow evaporation at room temperature.

Experimental details

Carbon-bound H atoms were placed in calculated positions (C–H 0.95Å for aromatic carbon atoms, C–H 0.99 Å for methylene groups) and were included in the refinement in the riding model approximation, with U_{iso}(H) set to 1.2U_{eq}(C). The H atoms of the methyl groups were allowed to rotate with a fixed angle around the C–C bond to best fit the experimental electron density (HFIX 137 in the SHELX program suite [6]), with U_{iso}(H) set to 1.5 U_{eq}(C). The H atom of the hydroxyl group was allowed to rotate with a fixed angle around the C–O bond to best fit the experimental electron density (HFIX 147 in the SHELX program suite [6]), with U_{iso}(H) set to 1.5 U_{eq}(O). The nitrogen-bound H atom was located on a difference Fourier map and refined freely.

Discussion

Olmesartan medoxomil is the most recent member of angiotensin receptor blockers, and a review on its pharmacokinetics and pharmacodynamics has been published recently [1]. Given its molecular set-up, it can act as a potential ligand for a variety of transition metals that, in combination with the title compound's inherent pharmacological activity, might open up the path for a large series of new metal-based drugs such as radiopharmaceuticals. Although the crystal structure of the title compound has been determined earlier [2], this study only reported metrical parameters about the molecule at room temperature without any discussion of structural features or intermolecular interactions whatsoever. The latter fact is an unacceptable starting point for the design of new drugs. In view of the importance of the title compound and at the beginning of a more comprehensive study about olmesartan medoxomil-based coordination compounds, we re-determined the molecular and crystal structure of the free ligand at low temperature to close this gap of knowledge and to allow for comparative studies in terms of metrical parameters as well as intermolecular forces in the crystal structures of envisioned reaction products. The two individual phenyl rings of the biphenyl moiety adopt a nearly staggered conformation with their planes intersecting at an angle of 50.77(6)°. The least-squares planes defined by the individual non-hydrogen atoms of the five-membered cyclocarbonate, imidazole system as well as the tetrazole moiety enclose angles of 44.55(8)°, 70.61(8)° and 26.07(7)°, respectively. A puckering analysis of the cyclocarbonate according to Cremer & Pople [3] is precluded by the small puckering amplitude (τ = 0.4°). In the crystal, intra- as well as intermolecular hydrogen bonds are observed. While the former ones are exclusively of the O–H···N type and are apparent between the hydroxyl group of the isopropyl group and the nitrogen atom of the imidazol moiety, the latter ones involve the nitrogen-bonded hydrogen atom of the tetrazole substituent and the oxygen atom of the isopropyl group. Apart from these classical hydrogen bonds, C–H···O contacts as well as C–H···N contacts

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are apparent whose range falls by more than 0.1 Å below the sum of van-der-Wals radii of the atoms participating in them. The C–H···N contacts appear between the methylene group adjacent to the cyclocarbonate functionality and one of the tetrazole's nitrogen atoms whereas the C–H···O contacts are supported by one of the hydrogen atoms on a phenyl group and the double-bonded oxygen atom neighbouring the imidazole group. In terms of graph-set analysis [4, 5], the descriptor for the classical hydrogen bonds is $S(5)R^2_2(30)$ on the unary level while the C–H···O and C–H···N contacts necessitate a $C^1_1(15)R^2_2(28)$ descriptor on the same level. In total, the molecules are connected to a three-dimensional network. The shortest intercentroid distance between two ring-centroids was found at 3.9960(8)Å and is apparent between the five-membered cyclocarbonate group and the phenyl ring bearing the tetrazol moiety.

Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	*x*	*y*	*z*	U_{iso}
H(1)	4*e*	0.5906	0.096	0.7268	0.088
H(1A)	4*e*	0.314(2)	–0.1777(9)	0.159(2)	0.056(5)
H(3)	4*e*	0.0936	–0.1994	–0.2060	0.044
H(4)	4*e*	0.0302	–0.1143	–0.3348	0.052
H(5)	4*e*	0.0359	–0.0129	–0.2518	0.052
H(6)	4*e*	0.0984	0.0031	–0.0384	0.043
H(9)	4*e*	0.0622	–0.1454	0.1992	0.033
H(10)	4*e*	0.0906	–0.1200	0.4105	0.032
H(12)	4*e*	0.2952	0.0216	0.3517	0.033
H(13)	4*e*	0.2632	–0.0022	0.1384	0.034
H(14A)	4*e*	0.1378	–0.0114	0.5558	0.032
H(14B)	4*e*	0.2160	–0.0715	0.5881	0.032
H(18A)	4*e*	0.5019	–0.0829	0.5931	0.051
H(18B)	4*e*	0.3788	–0.1045	0.6006	0.051
H(19A)	4*e*	0.5048	–0.1420	0.7758	0.074
H(19B)	4*e*	0.5425	–0.0712	0.8130	0.074
H(20A)	4*e*	0.3675	–0.0483	0.8534	0.122
H(20B)	4*e*	0.4178	–0.1077	0.9355	0.122
H(20C)	4*e*	0.3266	–0.1180	0.8117	0.122
H(22A)	4*e*	0.4977	0.1805	0.5197	0.068
H(22B)	4*e*	0.5158	0.2364	0.6205	0.068
H(22C)	4*e*	0.3933	0.2149	0.5587	0.068
H(23A)	4*e*	0.3519	0.1955	0.7789	0.072
H(23B)	4*e*	0.4749	0.2176	0.8370	0.072
H(23C)	4*e*	0.4319	0.1499	0.8718	0.072
H(25A)	4*e*	0.0964	0.2122	0.6654	0.045
H(25B)	4*e*	0.0627	0.1997	0.5173	0.045
H(29A)	4*e*	0.3008	0.3463	0.7912	0.074
H(29B)	4*e*	0.2038	0.2994	0.8113	0.074
H(29C)	4*e*	0.1794	0.3731	0.7912	0.074

Table 3. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	4*e*	0.58344(8)	0.13500(5)	0.7366(1)	0.0294(5)	0.0299(5)	0.104(1)	0.0034(4)	–0.0213(5)	–0.0217(6)
O(2)	4*e*	0.10837(7)	0.09214(4)	0.5314(1)	0.0277(4)	0.0323(5)	0.0507(6)	0.0005(3)	–0.0067(4)	–0.0060(4)
O(3)	4*e*	0.21963(7)	0.17456(4)	0.58946(9)	0.0261(4)	0.0223(4)	0.0500(5)	0.0041(3)	–0.0025(4)	–0.0025(3)
O(4)	4*e*	0.20850(9)	0.37806(4)	0.55429(9)	0.0551(6)	0.0285(5)	0.0419(5)	0.0014(4)	0.0091(4)	–0.0009(4)
O(5)	4*e*	0.14418(9)	0.29774(5)	0.43361(9)	0.0526(6)	0.0341(5)	0.0364(5)	0.0090(4)	0.0006(4)	–0.0034(4)
O(6)	4*e*	0.1786(1)	0.39006(6)	0.3435(1)	0.0867(9)	0.0518(7)	0.0466(6)	0.0114(6)	0.0157(6)	0.0122(5)
N(1)	4*e*	0.26766(9)	–0.20800(5)	0.1189(1)	0.0322(5)	0.0223(5)	0.0447(6)	–0.0023(4)	–0.0052(4)	–0.0028(4)
N(2)	4*e*	0.2887(1)	–0.26844(5)	0.1526(1)	0.0454(6)	0.0230(5)	0.0513(7)	–0.0003(4)	–0.0020(5)	–0.0007(5)
N(3)	4*e*	0.2127(1)	–0.30144(5)	0.0834(1)	0.0501(7)	0.0263(5)	0.0510(7)	–0.0065(5)	0.0022(5)	–0.0036(5)
N(4)	4*e*	0.1424(1)	–0.26377(5)	0.0053(1)	0.0406(6)	0.0293(5)	0.0455(6)	–0.0089(4)	0.0005(5)	–0.0073(5)
N(5)	4*e*	0.29991(8)	0.01007(4)	0.58940(9)	0.0272(5)	0.0199(4)	0.0265(4)	–0.0010(3)	0.0003(3)	–0.0028(3)
N(6)	4*e*	0.47114(8)	0.03793(5)	0.6678(1)	0.0281(5)	0.0228(5)	0.0443(6)	0.0025(4)	–0.0035(4)	–0.0041(4)
C(1)	4*e*	0.17825(9)	–0.20543(6)	0.0284(1)	0.0276(5)	0.0278(6)	0.0307(6)	–0.0043(4)	0.0033(4)	–0.0061(4)
C(2)	4*e*	0.13245(9)	–0.14953(6)	–0.0429(1)	0.0250(5)	0.0324(6)	0.0282(6)	–0.0016(4)	0.0020(4)	–0.0030(4)
C(3)	4*e*	0.0942(1)	–0.15831(7)	–0.1712(1)	0.0346(6)	0.0454(7)	0.0295(6)	–0.0041(5)	0.0031(5)	–0.0077(5)
C(4)	4*e*	0.0572(1)	–0.10773(8)	–0.2480(1)	0.0388(7)	0.0634(9)	0.0253(6)	0.0023(6)	0.0004(5)	0.0008(6)
C(5)	4*e*	0.0596(1)	–0.04778(8)	–0.1987(1)	0.0436(7)	0.0551(8)	0.0302(6)	0.0143(6)	0.0055(5)	0.0110(6)
C(6)	4*e*	0.0967(1)	–0.03844(6)	–0.0715(1)	0.0402(7)	0.0367(6)	0.0321(6)	0.0097(5)	0.0075(5)	0.0046(5)
C(7)	4*e*	0.13165(9)	–0.08883(6)	0.0090(1)	0.0269(5)	0.0297(6)	0.0265(5)	0.0020(4)	0.0032(4)	0.0003(4)
C(8)	4*e*	0.15893(9)	–0.07614(5)	0.1460(1)	0.0263(5)	0.0230(5)	0.0264(5)	0.0029(4)	0.0016(4)	–0.0003(4)
C(9)	4*e*	0.10881(9)	–0.11091(5)	0.2295(1)	0.0276(5)	0.0236(5)	0.0295(5)	–0.0048(4)	0.0008(4)	–0.0016(4)
C(10)	4*e*	0.12601(9)	–0.09597(5)	0.3554(1)	0.0275(5)	0.0229(5)	0.0278(5)	–0.0043(4)	0.0027(4)	0.0015(4)
C(11)	4*e*	0.19470(9)	–0.04598(5)	0.4026(1)	0.0235(5)	0.0189(5)	0.0268(5)	0.0011(4)	0.0005(4)	–0.0008(4)
C(12)	4*e*	0.24667(9)	–0.01191(5)	0.3207(1)	0.0298(5)	0.0201(5)	0.0325(6)	–0.0046(4)	0.0040(4)	–0.0019(4)
C(13)	4*e*	0.2282(1)	–0.02645(5)	0.1935(1)	0.0332(6)	0.0229(5)	0.0305(6)	–0.0025(4)	0.0075(4)	0.0025(4)
C(14)	4*e*	0.20675(9)	–0.03143(5)	0.5407(1)	0.0288(5)	0.0233(5)	0.0271(5)	–0.0057(4)	0.0029(4)	–0.0027(4)
C(15)	4*e*	0.30080(9)	0.07576(5)	0.6007(1)	0.0272(5)	0.0200(5)	0.0259(5)	0.0006(4)	0.0000(4)	–0.0040(4)
C(16)	4*e*	0.40910(9)	0.09132(5)	0.6511(1)	0.0272(5)	0.0219(5)	0.0332(6)	0.0017(4)	–0.0022(4)	–0.0045(4)
C(17)	4*e*	0.4040(1)	–0.00993(5)	0.6305(1)	0.0295(5)	0.0224(5)	0.0357(6)	0.0017(4)	0.0001(4)	–0.0028(4)
C(18)	4*e*	0.4408(1)	–0.07726(6)	0.6399(2)	0.0376(7)	0.0210(5)	0.0675(9)	0.0028(5)	0.0037(6)	–0.0020(6)
C(19)	4*e*	0.4791(2)	–0.09769(8)	0.7745(2)	0.0521(9)	0.0426(8)	0.086(1)	0.0066(7)	–0.0029(9)	0.0193(8)
C(20)	4*e*	0.3902(2)	–0.0925(1)	0.8503(2)	0.073(1)	0.087(2)	0.082(2)	0.002(1)	0.006(1)	0.031(1)
C(21)	4*e*	0.4699(1)	0.15265(6)	0.6938(1)	0.0262(5)	0.0237(5)	0.0536(8)	0.0015(4)	–0.0082(5)	–0.0102(5)
C(22)	4*e*	0.4691(1)	0.20035(6)	0.5888(2)	0.0405(7)	0.0273(6)	0.069(1)	–0.0059(5)	0.0089(7)	–0.0039(6)
C(23)	4*e*	0.4284(1)	0.18149(7)	0.8053(2)	0.0493(8)	0.0385(7)	0.0488(8)	0.0014(6)	–0.0089(6)	–0.0176(6)
C(24)	4*e*	0.19940(9)	0.11255(5)	0.5705(1)	0.0277(5)	0.0241(5)	0.0236(5)	0.0009(4)	–0.0009(4)	–0.0018(4)
C(25)	4*e*	0.1229(1)	0.21424(6)	0.5846(1)	0.0292(6)	0.0279(6)	0.0546(8)	0.0066(5)	0.0033(5)	–0.0012(5)
C(26)	4*e*	0.1544(1)	0.27922(6)	0.5596(1)	0.0332(6)	0.0288(6)	0.0374(6)	0.0086(5)	0.0027(5)	–0.0004(5)

Table 3. continued.

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(27)	4*e*	0.1931(1)	0.32734(6)	0.6313(1)	0.0396(7)	0.0282(6)	0.0381(7)	0.0046(5)	0.0064(5)	0.0001(5)
C(28)	4*e*	0.1774(1)	0.35883(7)	0.4338(1)	0.0519(8)	0.0363(7)	0.0412(7)	0.0109(6)	0.0082(6)	0.0008(6)
C(29)	4*e*	0.2217(2)	0.33736(8)	0.7677(1)	0.066(1)	0.0431(8)	0.0376(7)	–0.0024(7)	0.0062(7)	–0.0052(6)

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